PATENT

Appl. No. 09/322,259
Amdt. dated August 24, 2004
Reply to Office Action of October 16, 2003. A Notice of Appeal was filed April 14, 2004.

REMARKS/ARGUMENTS

Claim 1 was previously directed to preventive and treatment methods. The subject matter has now been divided into two independent claims. Claim 1 is directed to methods of treatment, and claim 82 to methods of prophylaxis (the term "preventing" has been replaced with prophylaxis as in other related cases). Support for prophylaxis is provided at e.g., p. 27, lines 12-14. New claims 82-102 correspond in part to claims 1-4, 6-8, 10-12, 14-15, 17, 21-24, 31, 32, and 35-37.

Claim 1 has also been amended to specify that the claim antibody is humanized, chimeric or a human monoclonal, and has human IgG1 isotype. Support for the recital of humanized, chimeric or human monoclonal is found in e.g., claims 10-12. Support for a human monoclonal is provided at e.g., p. 20, line 5. Support for a human IgG1 isotype is found at e.g., p. 21, lines 15-18. The previous recitation of a functional element in claim 1 of reducing levels of Aβ in the brain has been deleted in view of the Examiner's position that it does not confer patentable weight. No amendment should be construed as an acquiescence in any ground of rejection. Applicant addresses the Examiner's comment using the paragraph numbering of the office action.

¶5. Claim 5 stands rejected as being of improper dependent form. It is alleged that claim 1 already requires the patient and disease be characterized as having amyloid deposits. The recitation in claim 5 that the patient is asymptomatic is alleged to broaden claim 1. In response, it is noted that the recitation regarding amyloid deposits in claim 1 characterized the disease and not the patient. Thus, claim 5 was not inconsistent with claim 1. However, claim 5 has been cancelled as redundant in view of the amendment to direct claim 1 to therapeutic methods.

¶6. The Examiner has objected to Figure 11 as lacking an appropriate legend. Applicant submits a corrected Figure 11 herewith.

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¶¶7-8. The Examiner's comments are acknowledged. However, traverse of the species election is maintained for the reasons previously given. In any event, if the generic claim is allowed, it is requested that withdrawn species falling within the generic claim be reinstated under MPEP 809.02(c).

¶9. Newly submitted claim 56-58 and 60-81 stand withdrawn as directed to patentably distinct methods from the elected claims. In response, it is noted that claims 56-58 and 60-81 are dependent claims incorporating all the elements of elected claim 1 and specifying additional elements or steps. Therefore, claim 1 is related to claims 56-58 and 60-81 as genus and species. If generic claim 1 is allowed, it is requested that claims 56-58 and 60-81 be reinstated as species falling within an allowed generic claim under MPEP 809.02(c).

¶¶10-11. Claims 1-2, 4-8, 10-21, 24, 29-32 and 35-37 stand rejected as anticipated by Nettleship. Applicants disagree with the alleged basis for this rejection. However, the rejection is submitted to be moot in view of the amendment of the claims to specify that the antibody administered is chimeric, humanized or a human monoclonal, and is of human IgG1 isotype. Nettleship provides no discussion at all regarding the isotype of antibodies, and particularly does not teach selection of the claimed human IgG1 isotype. Further, although polyclonal sera may contain multiple isotypes, it does not contain chimeric or humanized antibodies, nor does it meet the requirement for a monoclonal human antibody. Thus, Nettleship does not disclose all elements of the present claims, and it is respectfully submitted that the rejection should be withdrawn.

¶12. Claims 1, 9, 13, 15 , 20 and 22-23 stand rejected as anticipated by Friedland. The Examiner alleges that Friedland teaches in vivo administration of murine monoclonal 10H3 to a mouse. The Examiner takes the view that Friedland's dosage of 10 micrograms corresponds to 10 mg/kg based on an average mouse weight of 10g. The rejection is respectfully traversed, particularly as applied to the amended claims.

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Applicant disagrees with the Examiner's comments for the reasons given in the previous response. Applicant also notes that an estimate of 10 g for a mouse is unduly low, the usual weight being about 50 g (see specification at p. 70, line 25). A dosage of 10 micrograms to a mouse of 50 g actually corresponds to a dosage of 0.2 mg/kg.

In any event, the rejection is moot in view of the amendment of the claims to specify that the antibody administered is chimeric, humanized or a human monoclonal, and is of human IgG1 isotype. The antibody used by Friedland was a mouse antibody, and therefore not of any human isotype.

The present claims are further distinguished from Friedland's discussion of administering antibody to a mouse in that the mouse used by Friedland neither had, nor was capable of developing, a disease characterized by amyloid deposits of Aβ. Normal mice do not develop such a disease; it is only specifically designed transgenic mice that can be used as models of Alzheimer's disease. Because the mouse used by Friedland neither had, nor was capable of developing, a disease characterized by amyloid deposits of Aβ, Friedland's use of the mouse cannot be considered a method of treatment or prophylaxis of the disease, as claimed.

¶¶13-14. Claims 1-2, 4-8, 10-24, 29-32 and 35-37 stand rejected as unpatentable over Nettleship under 35 USC 103(a). Applicant disagrees with the asserted bases for this rejection. However, the issues raised by the Examiner are submitted to be moot in view of the amendment of the claims to recite that the claimed antibodies is chimeric, humanized or a human monoclonal, and is of human IgG1 isotype. Although an understanding of mechanism is not required for practice of the invention, it is believed that this isotype is advantageous because it allows strongest binding to the human FcRI receptor on phagocytic cells, thereby promoting a clearing response of amyloid deposits by the phagocytic cells.

Nettleship would not have rendered obvious the above claims, because Nettleship provides no discussion of antibody isotype, much less any suggestion to use the human IgG1 isotype. It is noted that, the Examiner asserts that she is not required to supplement the teachings

of Nettleship insofar as Nettleship is deemed enabling. However, obviousness cannot be established by relying on the level of skill in the art to compensate for lack of motivation in Nettleship. "That which is within the capabilities of one skilled in the art is not synonymous with obviousness." *Ex parte Gerlach*, 212 USPQ 471 (Bd.App. 1980). An "assertion that one of ordinary skill in the relevant art would have been able to arrive at applicant's invention because he had the necessary skills to carry out the requisite process steps" is an "inappropriate standard for obviousness." *Orthokinetics Inc. vs. Safety Travel Chairs Inc.*, 1 USPQ2d 1081 (Fed. Cir. 1986). "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). Here, although the genetic engineering techniques needed to include a human IgG1 isotype may have been well known at the priority date of the claimed invention, the prior art does not suggest the desirability of the modification. Therefore, the present claims would not have been obvious in view of Nettleship.

¶15. Claim 1-2, 4 and 22-234 stand rejected as unpatentable over Walker under 35 USC 103(a). Walker is alleged to teach using the 10D5 antibody to label amyloid deposits in nonhuman primates. The Examiner takes the view that it would have been obvious to employ the same methodology in humans given the positive results in primates. This rejection is respectfully traversed.

The 10D5 antibody discussed by Walker is a mouse antibody. The isotype of this antibody is thus *mouse* IgG1. Not only is mouse IgG1, not a human isotype, it is not even the closest mouse equivalent of human IgG1. The closest mouse equivalent of human IgG1 is mouse IgG2a. Thus, Walker does not disclose or suggest an antibody having a human IgG1 isotype as claimed.

Further, it is submitted that Walker does not provide any reasonable expectation that antibodies could be used for in vivo diagnosis of Alzheimer's disease in a patient, let alone

treatment or prophylaxis of the disease, as claimed. Walker actually conducted his experiments on a rhesus monkey and injected his antibody directly into the CNS. Walker notes that the extent of labelling was incomplete ("intracistinernally injected antibody failed to reach a significant number of deposits") (at p. 382, second paragraph). Walker also notes that intracistinal injection or other techniques used to circumvent the blood brain barrier are "not suitable for routine therapeutic or diagnostic purposes" (at p. 382, second paragraph). Walker also considers the alternative route of delivering antibodies by the blood but implies that techniques for facilitating transport of large molecule across the blood-brain barrier first need to be developed or refined (id). Walker also states that the "blood-brain barrier prevents the passage of many types of molecules from the bloodstream to the brain . . . rendering vascular delivery of ligands to Aβ problematic" (at p. 377, first column, first paragraph). Walker concludes only that it "may eventually be feasible to employ antibodies to deliver therapeutic agents directly to Aβ in the brain, or in combination with imaging technologies, such as PET or SPECT, to diagnose β-amyloidoses in living subjects" (at p. 381, first column, second paragraph, emphasis supplied). The Examiner simply assumes Walker establishes the utility of the 10D5 antibody for diagnosis without addressing any of the above contrary teaching. Because of the limited results obtained by Walker, the potential difficulties envisaged by Walker in delivering antibody to humans, and the tentative nature of Walker's conclusion, one would not have reasonably expected Walker's approach could be used for diagnosis in humans without further invention.

Moreover, as discussed in the last response, a diagnostic method does not necessarily result in prophylactic or therapeutic treatment as specified in the pending claims. If an antibody were administered in a regime that achieved imaging, the same regime would not necessarily effect prophylaxis or treatment of Alzheimer's disease (or other disease associated with amyloid deposits of Aβ in the brain). *In vivo* imaging simply requires delivery of sufficient labeled antibody to generate a detectable image. It is not necessary that the antibody clear or prevent deposition of Aβ; indeed, if the antibody were completely successful in this regard, there would be nothing to label, thereby defeating the purpose of obtaining an *in vivo* image.

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For these reasons, withdrawal of the rejection is respectfully requested.

¶16. Claim 5 stands rejected as indefinite as not further limiting claim 1. This rejection appears to raise the same issue as that in paragraph 5 above. Applicant responds in the same way.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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